SJÖGREN’S SYNDROME

Autoimmune Epithelitis

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ABSTRACT

Sjögren’s syndrome is a chronic autoimmune disorder characterized by mononuclear cell infiltration proximally to epithelial cells of exocrine glands. In recent years, several studies have tried to address the function of the components of the immunopathologic lesion in Sjögren’s syndrome.

The majority of the mononuclear infiltrating cells are CD4 positive T lymphocytes (60–70%) whereas B cells constitute one fourth of the infiltrating cells. Macrophages and natural killer cells are poorly represented in the lesion. Epithelial cells of minor salivary glands of patients with Sjögren’s syndrome express proinflammatory cytokines (IL-1β, IL-6), protooncogenes (c-myc) and costimulatory molecules (B71, B72). The destruction of epithelial cells of Sjögren’s syndrome patients is probably due to activation of several apoptotic pathways since epithelial cells express different apoptosis related molecules such as Fas, FasL, Bax, while mononuclear cells express Bcl-2, Perforin and Granzymes. Finally epithelial cells seem to exert a regenerative effort since they express trefoil proteins (pS2).

The above properties give epithelial cells a significant role in the pathophysiology of the syndrome but the exact events which drive the immune system towards an autoimmune reaction remain obscure.

1. INTRODUCTION

Sjögren’s syndrome (SS) is a systemic autoimmune disorder characterized by chronic inflammation of the salivary and lacrimal glands, resulting in xerostomia and
keratoconjunctivitis sicca. In more than one third of the patients the disease may affect extraglandular sites like the kidneys, lungs, liver, blood vessels and lymph nodes. SS may exist as a primary condition or may be associated with other rheumatic and non-rheumatic autoimmune diseases (secondary SS). The two main immunologic abnormalities observed in SS are the lymphocytic infiltration of the affected tissues and the hyperreactivity of B cells as manifested by autoantibodies directed against organ and non-organ specific autoantigens [1].

2. CLINICAL ASPECTS OF THE SYNDROME

Clinically, SS affects the exocrine glands, thus the term “glandular SS” which includes symptoms of glandular dysfunction like dry eyes, mouth, nose airways, atrophic gastritis, subclinical pancreatitis and dry skin. In one-third of patients the lymphocytic infiltrates extend beyond the glandular sites and affect parenchymal organs such as the thyroid, liver, kidneys and lungs.

The histopathologic lesion of the kidneys resembles that seen in the exocrine glands (focal infiltrates around tubular epithelium which extend to the interstitium) resulting clinically in a tubular defect with or without acidosis [2]. Lung disease in SS has been previously described as slowly progressive involving mainly the airways and the interstitial space. Chest radiographs performed in 61 patients with SS revealed an interstitial pattern (27 patients) and a suspected interstitial pattern (21 patients). High resolution computerized tomography (HRCT) of the lungs, performed in 32 patients, disclosed thickened bronchial walls at the segmental level. Blood gases obtained from 44 patients revealed mild hypoxemia while the alveolo-arterial oxygen difference \[P(A - a)O_2\] showed a significant correlation with UEF$_{50}$ but not with DLCO (diffusing lung capacity), suggesting a small airway obstruction rather than a restrictive lung disease. Transbronchial biopsies performed in 11 patients showed that the predominant pathologic finding was bronchiolar lymphocytic infiltrates [3].

Liver involvement in SS is rare. The coexistence of elevated liver enzymes with circulating antimitochondrial antibodies suggests that liver pathology is similar to that of primary biliary cirrhosis [4].

The aforementioned observations of kidney, lung and liver involvement in SS patients (Table 1), strongly suggest that most of the extraglandular manifestations are due to attraction of lymphocytes by epithelial cells of renal tubules, bronchi and cholangia respectively, giving to epithelial cells an important role in the pathophysiology of the syndrome.

3. THE IMMUNOPATHOLOGIC LESION

The pathologic lesion observed in minor salivary glands (MSG) of patients with SS consists of round cell infiltrates that begin around ductal epithelial cells; whereas in advanced lesions the infiltrates extend and replace the functional tissue [1]. This results in acinar atrophy, duct dilatation, fibrosis and myoepithelial island formation. The majority of the infiltrating cells are T cells whereas B lymphocytes constitute one-fourth to one-fifth of the round cells. Analysis of the T cell population revealed that 60–70% of the T cells bears the CD4 phenotype, exhibit the memory/inducer marker (CD45RO) and express the adhesion molecule LFA-1 (lymphocyte function associated molecule) [5]. LFA-1 is a cell surface glycoprotein that has been associated with adhesion of lymphocytes,